In order to expedite prosecution of certain preferred embodiments, and without acceding to the correctness of the rejection, each of the independent claims (i.e., claims 1 and 2) have been amended to incorporate these limitations. Specifically, each of claims 1 and 2 have been amended to recite that the "OP/BMP renal therapeutic agent comprises a dimeric protein having an amino acid sequence having at least 70% amino acid sequence homology with the C-terminal seven-cysteine skeleton of human OP-1, amino acids 330-431 of SEQ ID NO:1" and "induces chondrogenesis in an *in vivo* ectopic bone assay." SEQ ID NO: 1 has been added to the specification and corresponds to SEQ ID NO: 2 of U.S. Pat. No. 5,266,683. Support for the amendments may be found in the definition of a "renal therapeutic agent" on page 8, lines 4-22, and the description of the C-terminal seven cysteine domain of human OP-1 at page 16, lines 1-6.

The amendment to claim 1 rendered claim 5 redundant, as it merely repeated the 70% homology limitation. Therefore, claim 5 has been canceled and the dependencies of claims 6-10 have been corrected such that they depend from claim 1.

Similarly, the amendment to claim 1 rendered part (a) of claim 11 redundant, as it merely repeated the ectopic bone assay limitation. Claim 11 has been canceled.

Applicants respectfully submit that the amendments to the claims overcome the grounds for the rejection under 35 U.S.C. §112, first paragraph, and therefore request reconsideration and withdrawal of the rejection.

Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 1-17, 24, 28 and 32 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The various bases for these rejections are discussed separately below.

Claims 1-17, 24, 28 and 32 were rejected for lacking a process step or a recitation of a result to be achieved. In order to expedite prosecution of certain preferred embodiments, and without acceding to the correctness of the rejection, each of the independent claims (i.e., claims 1

and 2) are amended herein to recite that the administration of a therapeutically effective amount of the OP/BMP renal therapeutic agent "causes a clinically significant improvement in a standard marker of renal function in said mammal." Support for the amendment can be found in the definition of "therapeutic efficacy" on page 8, line 23 to page 9, line 10. Applicants respectfully submit that the amendments to the claims overcome this ground for the rejection under 35 U.S.C. §112, second paragraph, and therefore request reconsideration and withdrawal of the rejection.

Claims 1-17, 24, 28 and 32 were rejected for reciting a "therapeutically effective amount" without a process step or a recitation of a therapeutic effect. As noted in the previous paragraph, claims 1 and 2 are amended herein to recite a therapeutic effect. Therefore, Applicants respectfully submit that the amendments to the claims overcome this ground for the rejection under 35 U.S.C. §112, second paragraph, and therefore request reconsideration and withdrawal of the rejection.

Claims 1, 11-17, 24, 28 and 33 were rejected for reciting an "OP/BMP renal therapeutic agent" without identifying the material element or combination of elements which is unique to and definitive of the agent. As noted with respect to the rejections under 35 U.S.C. §112, first paragraph, claims 1 and 2 are amended herein to recite both structural and functional limitations of the useful agents. Therefore, Applicants respectfully submit that the amendments to the claims overcome this ground for the rejection under 35 U.S.C. §112, second paragraph, and therefore request reconsideration and withdrawal of the rejection.

Claims 3-10 were rejected for reciting the term OP-1 without identifying the material element or combination of elements which is unique to and definitive of the agent. Respectfully, OP-1 was well known in the art at the time the application was filed, as evidenced by the numerous references provided with Applicants' Information Disclosure Statement, including the Kuberasampath et al. reference (BB) cited by the Examiner against the present claims. In addition, the Specification provides specific references for the structure of OP-1 (page 15, line 4-6). Patent applicants are not required to disclose in the Specification information that is well known in the art. Nonetheless, Applicants have, for other reasons, amended the Specification to

include the normal, human OP-1 sequence. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, second paragraph.

Claim 3 was rejected for reciting the terms "OP-2", "OP-3", "BMP2", "BMP3", "BMP4", "BMP5", "BMP6", and "BMP9" without identifying the material elements or combinations of elements which are unique to and definitive of these agents. Respectfully, each of these proteins was well known in the art at the time the application was filed, as evidenced by the numerous references provided with Applicants' Information Disclosure Statement. In addition, the Specification provides specific references for the structure of these proteins (page 15, line 4-12). Patent applicants are not required to disclose in the Specification information that is well known in the art. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, second paragraph.

Claim 12 was rejected for reciting the term "human osteogenic proteins and human bone morphogenetic proteins" without identifying the material elements or combinations of elements which are unique to and definitive of these agents. Respectfully, the human osteogenic proteins (e.g., OP-1, OP-2, OP-3) and human bone morphogenetic proteins (e.g., BMP2, BMP3, BMP4, BMP5, BMP6, etc.) were well known in the art at the time the application was filed, as evidenced by the numerous references provided with Applicants' Information Disclosure Statement. In addition, the Specification provides specific references for the structure of these proteins (page 15, line 4-22). Patent applicants are not required to disclose in the Specification information that is well known in the art. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, second paragraph.

Claims 5-11 were rejected for reciting "said renal therapeutic agent" without sufficient antecedent basis. The Examiner suggested amending this phrase to "said OP/BMP renal therapeutic agent." Claims 5 and 11 are canceled herein. However, the limitation of claim 5 has been added to claims 1 and 2 and the suggested language is employed in these amended claims. In addition, claims 6-10 are amended herein to conform with amended claim 1. Therefore, Applicants respectfully submit that the amendments to the claims overcome this ground for the

rejection under 35 U.S.C. §112, second paragraph, and therefore request reconsideration and withdrawal of the rejection.

Claims 3-4 were rejected for reciting "a C-terminal cysteine domain" without identifying the material element or combination of elements which is unique to and definitive of this domain. Respectfully, the meaning of "C-terminal cysteine domain" of the OP/BMP family of proteins was well known in the art at the time the application was filed, as evidenced by the numerous references provided with Applicants' Information Disclosure Statement. In addition, the Specification specifically teaches that the C-terminal cysteine domains of these proteins are 97-106 residue sequences within the mature proteins, and include the six or seven conserved cysteine residues which characterize the family (page 13, line 25 through page 14, line 6). As an example, and preferred embodiment, the C-terminal cysteine domain of human OP-1 is described by reference to a specific sequence (page 16, lines 5-6). The Specification also provides specific references for the structures of the other OP/BMP proteins (page 15, line 4-22) and one of ordinary skill in the art can easily align them with the OP-1 sequence to identify the C-terminal cysteine domains of these other proteins. Patent applicants are not required to disclose in the Specification information that is well known in the art or which would be obvious to one of skill in the art. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, second paragraph.

Claims 3 and 4 were rejecting for reciting the indefinite phrase "consisting at least." Claims 3 and 4 are amended herein to recite the open-ended phrase "comprising at least." Therefore, Applicants respectfully submit that the amendments to the claims overcome this ground for the rejection under 35 U.S.C. §112, second paragraph, and request reconsideration and withdrawal of the rejection.

Claims 5-11 were rejected for reciting "a C-terminal cysteine domain of human OP-1" without identifying the material element or combination of elements which is unique to and definitive of this domain. Claims 5 and 11 are canceled herein. Claims 6-10 now depend directly from claim, and claim 1 is amended herein to make specific reference to the "C-terminal cysteine

domain of human OP-1" as residues 330-341 of SEQ ID NO:1. Therefore, Applicants respectfully submit that the amendments to the claims overcome this ground for the rejection under 35 U.S.C. §112, second paragraph, and request reconsideration and withdrawal of the rejection.

Rejections Under 35 U.S.C. §102

Claim 2 was rejected under 35 U.S.C. §102(b) as being anticipated by Kuberasampath et al. (reference BB). The Office Action states that Kuberasampath et al. discloses "administering to a mammal a therapeutically effective amount of an OP/BMP renal therapeutic agent."

For anticipation under 35 U.S.C. §102, a reference must teach every aspect of the claimed invention either explicitly or impliedly. Any feature not directly taught must be inherently present. MPEP 706.02. A rejection based on 35 U.S.C. §102(b) can be overcome by persuasively arguing that the claims are patentably distinguishable from the prior art, or by amending the claims to patentably distinguish over the prior art. MPEP 706.02(b).

Kuberasampath does not teach a method to delay the need for, or reduce the frequency of, chronic dialysis treatments. In addition, Kuberasampath does not teach a method, as recited in claim 2 as amended herein, wherein administration of a therapeutically effective amount of an OP/BMP renal therapeutic agent "causes a clinically significant improvement in a standard marker of renal function". Therefore, Kuberasampath does not teach or disclose all of the limitations of claim 2, as amended, and cannot anticipate the claimed subject matter. Applicants respectfully request, therefore, that the rejection be reconsidered and withdrawn.

Rejections Under 35 U.S.C. §103

Claims 1-17, 24, 28, and 32 were rejected under 35 U.S.C. §103(a) as being unpatentable over Glassock et al. (reference V) and Brenner et al. (reference U) in view of Kuberasampath (reference BB).

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available in the art, to modify the references or to combine the references' teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). MPEP 706.02(j).

Respectfully, Applicants submit that there is no suggestion or motivation in the references, or in the knowledge generally available in the art at the time the invention was made, that OP/BMP family proteins could be used in methods of treating chronic renal failure. First, there is clearly no such teaching in the references themselves. Moreover, the mere facts that some renal injuries are due to immunologic processes, that some renal injuries progress to chronic renal failure, and that OP-1 is one molecule capable of modulating an inflammatory response, does not add up to a motivation to administer OP/BMP family proteins to mammals in, or at risk of, chronic renal failure.

Second, the references, alone or in combination, do not provide a reasonable expectation that the administration of OP/BMP family proteins could cause a clinically significant improvement in a standard marker of renal function in said mammal, as required by the amended claims. To hold otherwise would be to suggest that, based on Glassock and Brenner, each and every agent capable of modulating an inflammatory response can reasonably be expected to do the same.

Finally, the references, alone or in combination, fail to teach or suggest the limitations that that administration of a therapeutically effective amount of an OP/BMP renal therapeutic agent can cause a clinically significant improvement in a standard marker of renal function (all claims); can be used to treat end-stage renal disease, chronic diabetic nephropathy, diabetic glomerulopathy, diabetic renal hypertrophy, hypertensive nephrosclerosis, hypertensive

glomerulosclerosis, hereditary nephritis, and renal dysplasia (claim 13); can be used to treat glomerular hypertrophy, tubular hypertrophy, glomerulosclerosis, and tubulointerstitial sclerosis (claim 14); can be used to treat renal fibrosis (claim 15); should be administered when a mammal possesses a number of functional nephron units which is less than about 50% of a number of functional nephron units present in a mammal having intact healthy kidneys claim 17); should be administered when a mammal has a GFR which is chronically less than about 50% of a GFR_{exp} for said mammal (claim 24); should be administered when a human male weighing at least about 50 kg has a GFR which is chronically less than about 50 ml/min (claim 28); or should be administered when a human female weighing at least about 40 kg has a GFR which is chronically less than about 40 ml/min.

Respectfully, therefore, Applicants submit that the rejection under 35 U.S.C. §103 is improper, and request reconsideration and withdrawal of the rejection.

SUMMARY

Claims 1-17, 24, 28 and 32 were pending in the Application. Claims 5 and 11 are canceled, and claims 1-3 and 6-10 are amended by the present Amendment. Applicants respectfully submit that no new matter is introduced by the present Amendment.

Applicants request that the Examiner reconsider the application in light of the foregoing Amendment and Response, and respectfully submit that the claims, as amended, are in condition for allowance. If, in the Examiner's opinion, a telephonic interview would expedite the favorable prosecution of the present application, the undersigned attorney would welcome the opportunity to discuss any outstanding issues, and to work with the Examiner toward placing the application in condition for allowance.

The fee for a five-month Extension of Time for Response is submitted herewith. Applicants believe that no additional fees are necessitated by the present Amendment. However, in the event that any additional fees are due, the Commissioner is hereby authorized to charge any such fees to Attorney's Deposit Account No. 20-0531.

Respectfully submitted,

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